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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/018,962	12/18/2001	Fumio Itoh	2618 USOP	6020

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TAKEDA PHARMACEUTICALS NORTH AMERICA, INC
INTELLECTUAL PROPERTY DEPARTMENT
475 HALF DAY ROAD
SUITE 500
LINCOLNSHIRE, IL 60069

EXAMINER	
BERNHARDT, EMILY B	

ART UNIT	PAPER NUMBER
1624	9

DATE MAILED: 06/12/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 10/018,962	Applicant(s) ITOH et al.
	Examiner Emily Bernhardt	Art Unit 1624

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on 5/9/03 .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) 1-50 is/are pending in the application.

4a) Of the above, claim(s) 12-15 and 34-44 is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) 1-11, 16-26, 28-33, and 45-50 is/are rejected.

7) ☒ Claim(s) 27 is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 3 & 6
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Applicants' election with traverse of Group I and in particular species of eg.38 in paper no.8 is acknowledged but is not persuasive for the following reasons. The traverse is directed to the separation of group I from corresponding subject matter (presumably, piperazines) in Groups V-VII. For V only one process of making is considered to form part of the same invention with corresponding final products as set forth in 37 CFR 1.475(d). For group VI the starting materials therein lack the essential structural elements present in final products as both the sulfonyl group and X2-Q3 group are absent and the compounds do not make all of final products of I only A as NR3. Additionally, said compounds are not employed as direct precursors to the final products as can be seen in the alternate processes of manufacture being claimed. Subject matter of VII is not completely defined but only requires the middle fragment of group I compounds be present in any mixture that is an enzyme inhibitor. This feature appears to be old as evidenced by the many "X" references cited in applicants' international search report against one or more claims within this group.

Accordingly, the lack of unity requirement is deemed proper and is therefore made FINAL .

To clarify the record claim 15 was inadvertently included as part of Group I. Said claim properly belongs only in Group IV as already indicated. ~~This~~ Thus in Group I the claims should read as: 1-11, 16-33 and 45-50. It has been so corrected on the PTO's copy.

Claims 1-10,16-26, 29-33 and 45-50 are rejected under judicial doctrine as being drawn to an improper Markush group. The Markush at R1/R2 (at the very least) when viewing the compounds as a whole clearly demonstrates the widely divergent compounds embraced and not a recognizable class of compounds in a specific pharmaceutical area. Note In re Winnek 73 USPQ 225 and In re Milas 71 USPQ 212 and In re Ruzicka 66 USPQ 226 in which a similar holding was upheld. Limiting the claims to the elected invention would overcome this rejection.

The amendment filed 12/18/01 is objected to under 35 U.S.C. 132 because it introduces new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is as follows: The replacement of "benzindazolyl" with "benzimidazolyl" on p.29. While applicants refer to a "typographical error", a specification cannot be corrected unless it is obvious what

is wrong and what the specification should have read. See for example, Ex parte Bondiou 132 USPQ 356 . Applicants do not point to any species exemplifying the ring system now recited. The examiner cannot find this ring system in any other section of the specification relating to "aromatic heterocyclic groups".

Applicant is required to cancel the new matter in the reply to this Office Action.

Claims 1-11,16-26, 29-33 and 45-50 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The generic claims cover the newly added ring inserted in the specification on p.29 as discussed above and thus the claims' scope has been broadened from that originally filed.

Claims 1-11,16-26,28-33,45-50 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. Terms defining the variables in main claim 1 and in the dependent claims are not readily ascertainable as to scope. The definitions beginning on p.19 of the specification are invariably open-ended having "for example," included in the broadest definition for each term. See "optionally substituted", "hydrocarbon group", "heterocyclic group",etc. Within the scope of hydrocarbon groups alone, the alkyl, alkenyl,alkynyl, cycloalkyl ranges are not clearly set forth in view of the open-ended definition. For acyl the only information clearly indicating structure is that it can be S(O)(O) or C(O) but to what these atoms are attached is not clearly defined. There appears to be no concise definition for Y rings as choice (1) or (3). Note In re Wiggins 179 USPQ 421 regarding such terminolgy.

2."Prodrug" appearing in claim 2 and claim 27 is outside the scope of main claim 1. Additionally, while specification describes exemplary groups as prodrugs for various functional groups that can be present, a second alternate definition is mentioned by way of a Japanese textbook which cannot be relied on as completing the instant disclosure (see below objection/rejection based on improper incorporation).

3. R as a halogen atom is embraced in claim 3 which is outside the scope of claim 1.

4. Claims 30-32 do not further limit the scope of claim 29 since different intended uses in such claims (i.e. composition claims) are given no material weight. See In re Tuominen 13 USPQ 89.

5. In claim 45 The "a" on 1st line should be omitted since it does not read well grammatically.

6. Claim 46 is of indeterminate scope as there is no art-recognized disorder known as "inhibiting an activated coagulation factor X". Defining a disease(s) by its (their) underlying cause renders the scope of intended uses indeterminate since the claim language may read on diseases not yet known to be caused by or affected by such action or in ways not yet understood. Additionally, determining whether a given disease responds or not to factor X inhibitors involves much experimentation since a negative response from one patient does not mean the drug isnt useful as no drug has 100% effectiveness. Thus what "success rate" determines if a particular inhibitor is effective and how many patients (and dosage regimens) need to be tested? The test for determining compliance with 35 USC 112, par.two is whether applicants have clearly defined "their" invention not what may be discovered by future research as this type of claim language clearly requires.

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 48-50 are rejected under 35 U.S.C. 101 because claims drafted in terms of use have been held to be non-statutory. See Clinical Products v. Brenner 149 USPQ 475.

The incorporation of essential material in the specification by reference to a foreign application or patent, or to a publication is improper. Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or a practitioner representing the applicant, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. See *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973); *In re Hawkins*, 486 F.2d 579, 179 USPQ 163 (CCPA 1973); and *In re Hawkins*, 486 F.2d 577, 179 USPQ 167 (CCPA 1973).

The attempt to incorporate subject matter into this application by reference to a textbook on p.74-75 is improper because the subject matter being referenced is essential material being claimed in some of the dependent claims. MPEP 608.01(p) precludes reliance thereon.

Claims 1-11, 16-26,28-33 and 45-50 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

1).Specification provides no adequate support teaching how to use **representative** scope of instant elected piperazinone compounds which can carry from a reading of the specification a nonlimiting array of hydrocarbon groups as well as heterocyclic groups at every location (except D) including optionally substituted groups which in turn are further substituted with more many more functional groups as described beginning on p.19 of the specification through p.61. Compounds made do not represent such a scope since most have a halonaphthyl as R with a few benzopyranyl,benxoxepinyl, and one or two being

benzothienyl,thiazolyl,benzofuryl,quinolinyl and only 2 examples of bicyclic-fused hetero rings. When not halo-substituted the only other substituents seen on thes rings are N(H)Ac, lower alkyl(Me). When not naphthyl as a "hydrocarbon group", the only other examples are indenyl or phenylvinyl with halo,vinyl, alkoxy, or alkoxyalkoxy as substituents. When A is a singly bonded N the only R3 choices made are H,alkyl,lower acyl, C3 alkenyl, or CH2-COOEt. Y is always piperidino with most of species having as Z a pyridyl either unsubstituted or substituted with typical groups such as halo, alkyl,amino,loweralkylamino, hydroxyalkyl, alkoxyalkyl, carbamoylalkyl, aminoalkyl. When not pyridyl Z as quinolinyl was prepared as well as a 2-NH2 pyrimidyl. The only imidoyl group as Z prepared is -C=N(H)Me. Substiuents on piperazinone when present are only present once with groups such as alkyl, carboalkoxy, hydroxymethyl, aminomethyl, carboalkoxymethyl or 3 saturated azine rings attached via a carbonyl.

However no test data has been presented (only testing protocols) and thus no clear evaluation of which functional groups at various positions out of the many claimed might affect potency to a large or small degree. Thus, there is no reasonable basis for assuming that the myriad of remaining compounds which easily totals in the

billions embraced by the generic claims will all share the same physiological properties since they are so structurally dissimilar as to being chemically and biologically non-equivalent and there is no basis in the prior art for assuming the same. Note In re Surrey 151 USPQ 724 regarding sufficiency of disclosure for a Markush group. Also see MPEP 2164.03 for enablement requirements in cases directed to structure-sensitive arts such as the pharmaceutical art. Also note the criteria for enablement as set out in In re Wands cited in MPEP 2164.01(a), August 2000 edition. Thus given the breadth of the claims, the level of unpredictability in the art and the lack of direction (i.e. working examples) provided as to what other derivatives might work, this rejection is being applied; 2) Applicants provide no reasonable assurance that any and all "prodrug" derivatives of instant compounds will have the ability to generate the instant compounds in vivo by one or more processes. Additionally method claims include such moieties. Generally, prodrugs themselves are not considered to be therapeutically active but only to provide the active compound in vivo. Distinguishing whether a compound is a prodrug or a drug in its own right is a difficult matter.

Claim 27 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. No art was found based on the classification of the species embraced in this claim.

Any inquiry concerning this communication should be directed to Emily Bernhardt at telephone number (703) 308-4714.

A facsimile center has been established for Group 1600. The hours of operation are Monday through Friday, 8:45 AM to 4:45 PM. The telecopier numbers for accessing the facsimile machine are (703) 308-4556 or (703) 305-3592.

E Bernhardt

EMILY BERNHARDT

PRIMARY EXAMINER

GROUP 1600